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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/554,567	09/01/2000	Adriano Aguzzi	6458.US.01	2914

7590 09/21/2005

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EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/554,567	AGUZZI ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 8, 2004 has been entered.

The amendment filed July 8, 2004 in response to the Office Action of December 10, 2004 is acknowledged and has been entered. Claims 35-37 are pending and are currently being examined.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Please Note in this case Applicants have amended the claims but the claim amendments do not effect the rejection as the claims are rejected for the same reasons as in the prior Office actions. In this case the claim amendment do not materially alter the claim limitations. The amendments merely clarify the prior claims. For instance the addition "suspected of TSE infection" this limitation is obvious because there is no reason to test a sample unless the sample is thought to potentially contain TSE. Therefore, the "suspected of TSE infection" limitation does not materially alter the claim. The limitation "identifying TSE infected cells based on the presence of said signal and wherein the identification of TSE-infected cells is associated with TSE promulgation and primary infection" this limitation also does not materially alter the claim, it merely serves as a resolution step that reads back on the preamble. The instant amendments serve to clarify the claim but do not materially alter the claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 103

The rejection of claims 35-37 under 35 U.S.C. 103(a) as being unpatentable over O'Rourke et al. (US Pat No. 6,165,784) and/or Korth et al. (Nature 6 November 1997; 390:74-77), in view of Kuroda et al. (Infection and Immunity 1983; 41:154-61) and/or Manuelidis et al. (Science 1978; 200:1069-1071) **is maintained** for reasons of record.

Applicants' arguments have been fully considered but have failed to persuade the Office to remove the instant rejection.

Applicants' reassert that the cited references of Kuroda et al. or Manuelidis et al. referred to the disease causing agent as being a virus instead of the instantly claimed prion protein (TSE infecting agent). The protein only theory of disease has only recently gained acceptance in the scientific community. The biochemist, Stanley Prusiner, whose discovery provided key insights into dementia-related diseases, won the 1997 Nobel Medicine Prize, Sweden's Karolinska Institute. The institute said Prusiner's work helped the world to understand more about Alzheimer's and Mad Cow disease through his discovery of the prion, a disease-causing agent like bacteria or viruses. Even today there are is still a small group scientists that do not believe the protein only theory. Both of the cited references were published at a time when the prion protein theory of disease was not generally accepted. Even if the references erroneously referred to the disease-causing agent as a virus this does not detract from the important observation made in the references.

Applicants assert that the inventors are the first to determine the different roles of different components of the immune system by using a panel of immunodeficient mice inoculated with prions. Applicants meticulous dissection of the roles of B and T cells using more sophisticated methodologies and reagents does not take away from the observations in the prior art that have associated TSE (CJD or scrapie) with the B and T cells fractions obtained from the spleen of infected animals. In this instance the claims are drawn to a method of detecting the presence of the infective agent in the B and T cells from a patient test sample. The

prior art has shown that the CJD or scrapie agent is associated with these cells. Thus, Applicants arguments are not persuasive.

Applicants assert that other references than those cited in the instant rejection teach away from the instant invention, citing Lasmezas (Journal of Virology, 1996), O'Rourke (Journal of General Virology), Bueler (nature, 1992) and Blattler (1997). Applicnat asserts that these references do not provide any insight as to the role of B-cells and T-cells in TSE or any other specific cells within the lymphoreticular system (LRS).

> A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley,* 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). General skepticism of those in the art – does not amount to teaching away -- is also "relevant and persuasive evidence" of nonobviousness. *Gillette Co. v. S.C. Johnson & Son, Inc.* , 919 F.2d 720, 726, 16 USPQ2d 1923, 1929 (Fed. Cir. 1990). In effect, "teaching away" is a more pointed and probative form of skepticism expressed in the prior art. In any case, the presence of either of these indicia gives insight into the question of obviousness.

> A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." See *In re Gurley*, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

Here in contrast to Applicant's assertions of teaching away by the prior art the prior art actually provides further evidence that T and B cells are important in the TSE infectivity:

O'Rourke et al. (Journal of General Virology) teaches that SCID mice which lack functional follicular dendritic cells and do not have lymphocytes. CB17-SCID mice are a results of mutations on chromosome 16, these mice lack an inability to rearrange VDJ segments and thus their humoral (B-cell) and cellular (T-cell) immune system fails to mature. Thus, these mice do not have function B and T cells. The reference indicates that the scrapie agent does not

replicate in the spleen of the SCID mouse and they theorized that this lack of infectivity could be due to the lymphocyte deficiency, lack of follicular dendritic maturation or some other defect in the SCID mouse. Thus, the reference implicates B and T cells or follicular dendocytes as harboring scrapie infective agent by showing that animals which do not have B and T cells do not have scrapie agent present in their spleen. Therefore, the reference does not teach away from the instant invention as Applicants assert.

Lazmezas et al. teaches that PrPres was detected in CB17 control mice and reconstituted SCID mice but not in SCID mice alone. Here the SCID mice were reconstituted with the spleen cells (containing function T and B cells) from the normal CB17 mice (see abstract and table 1). Thus the reference adds to the knowledge that cells from the spleen are important for the transmission of TSE. Spleen cells comprise a high number of B and T cells in addition to other cells. Therefore, the reference does not teach away from the instant invention as Applicants assert.

Blattler et al. teaches that prion deficient mice do not accumulate PrP in their spleen. Yet in mice with reconstituted bone marrow (ie cells that can express PrPC) the spleens accumulates prion to their wild type levels. Thus reconstitution of the host lymphohaemopoitic system was sufficient to reconstitute the spleen accumulation. The reference did observe that the neurographs did not receive any prion peripheral infection. The lack of establishing prion in the neurographs has three possible explanations: "(1) prions administered peripherally must first replicate in peripheral organs from where they invade the central nervous system (2) prion spread is possible in the absence or PrPC but does not occur in Prnp0/0 mice owing to the humoral immune response to PrP that occurs in such animals (3) whether they replicate ort not prion need

a continuous chain of PrPC – expressing tissues for centripetal propagation in the host." (see page 69, column 2, 3r paragraph). Thus the reference indicates that upon reconstitution of lymphocytes (with the bone marrow) the spleen cell accumulation of prion returned to wild type level indicating that these cells play an important role in the prion infection cycle. Therefore, the reference does not teach away from the instant invention as Applicants assert.

Bueler et al. teach that PrPC is a host protein that is anchored on the outer surface of neurons and to a lesser extent on lymphocytes and other cells. Although the function of PrPC is not known the observation has been made that in animals without PrPC do not propagate scrapie. The reference teaches "that PrPC is expressed on the surface of B and T cells." Thus it is not clear how this reference teaches away from the instant invention.

Applicants arguments that the references cited in the specification teach away from the instant invention and thus would not make the invention obvious over the cited art is not convincing for the reasons set out above.

In response to Applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the animal experiments by Kuroda et al. and Manuelidis et al. show that the disease causing agent is found in B and T cells of infected animals, regardless of what the investigators think the actual infective agent may be. The method of detecting the infecting agent in the

experiments was to inject the fractionated samples into disease free animals. The experiments clearly show that the disease-causing agent is present in the T and B cells. The O'Rourke et al. and Korth et al. references disclose using a different method of detecting the disease-causing agent, with antibodies. This method of detection is relatively simple to administer by laboratory personal, direct, time efficient and does not require lengthy incubations periods.

Kuroda et al. in 1983 fractionated B cells and T cells from diseased animals and inoculated the fractionated samples into non-diseased animals. The experiments indicate that the disease causing agent obtained from the spleens of mice infected with the causative agent of Creutzfeldt-Jakob disease (CJD), can be injected into susceptible mice and transmit disease (see entire document, especially Tables 2 and 4). The method used in the reference is a) collect the spleen from a CJD infected mouse, b) obtain lymphocytes from the spleen, c) fractionate into B and T cells, d) inoculate mice tot detect infective agent. Thus Kuroda et al. teach a method to test for the presence of TSE agent in an infected animal (an animal suspected of TSE infection).

Manuelidis et al. in 1978 established that collecting B cells and T cells from infected animals, by isolating the buffy coat (contains B and T cells), and injecting the buffy coat into disease free animals (guinea pigs) and observing the animals for the progression of the disease. The reference indicates that an earlier article showed that scrapie replicates in "lymphocytic tissue" (spleen, lymph nodes, thymus) after subcutaneous inoculation in mice (see 170, column 3, 3rd paragraph). Manuelidis et al. theorized that maximal infectivity should reside in the buffy coat (white blood cells) rather than in the serum or red blood cells (see 170, column 3, 3rd paragraph). This reference established directly that the disease-causing agent is found in the buffy coat (contains B and T cells) of blood. The reference also indicated that the hematogenous

spread is implicated in man (see last paragraph) indicating that this could have implications of the blood banking system.

O'Rourke et al. tests for TSE in lymphoid tissue using an antibody that serves as a ligand in various immunoassays, including immunohistochemistry, western immunoblots, and dot blots (see entire document, e.g., "Summary of the Invention"). O'Rourke et al. teach that antibody ligands may be either polyclonal sera or monoclonal antibodies (see entire document, e.g., column 5, especially lines 40-50). The reference teaches the detection steps of starting with tissue homogenization, treatment with proteinase K, separation on polyacylamide gel, transfer to a filter and contacting the filter with a monoclonal antibody to detect the presence of prion in the tisse sample (see column 6, lines 45-55). The reference used TSE containing aliquots equivalent to 125 mg starting material were electrophoresed through a 15% polyacrylamide mini-gel and transferred to PVDF membranes. The filters were developed with monoclonal antibody or a control antibody, goat anti-mouse IgG-HRPO, and a chemiluminescent substrate (see column 10, lines 34-65). The presence of a signal is indicative that prion protein was present in the sample.

Korth et al. detects TSE based upon a monoclonal antibody that is specific for the prion form of PrP (the causative agent in TSEs) versus the cellular form of PrP (see entire document, e.g. Abstract). Korth et al. teach that this antibody can be used to identify the prion form of PrP directly, thus providing a basis for a TSE test in living humans or animals, by lowering the detection threshold needed (see especially paragraph preceding "Methods" on page 77). The reference teach the following steps a) taking brain (tissue) and homogenizing the sample, b) followed by immunoprecipitation with a monoclonal antibody, c) digesting the sample with proteinase K, d) boiling sample in SDS-page buffer, separating on a gel and transferring to

membrane (Western Blot), e) detecting the prion on the Western-blot using a rabbit anti-PrP antibody. Complex formation on the Western blot is indicative of the presence og prion in the brain (tissue) sample.

Thus Kuroda et al. teach that both B cells and T cells can transmit TSE, and Manuelidis et al. teach that it is important to focus on these cellular populations (buffy coat) to increase the sensitivity of assays for TSE infectivity. Both O'Rourke et al. and Korth et al. teach methods of detecting the disease form of prion protein after proteinase K digestion followed by SDS-Page electrophoresis and blotting onto a membrane. One of ordinary skill in the art would have had a high expectation of success in applying the techniques taught by O'Rourke et al. or Korth et al. to the infected tissue disclosed by Kuroda et al. or Manuelidis et al. It would have been obvious at the time the invention was made to improve the sensitivity of the TSE tests by collecting samples containing B cells and/or T cells and testing for the presence of TSE using an antibody-based system. The ordinary artisan at the time the invention was made would have been motivated to this in order to avoid having to utilize animals in order to test for infectivity in the B and/or T cell population. The ordinary artisan at the time the invention was made would have reasonably expected that concentrating a cell type known to be infected with the TSE agent would increase the sensitivity of detection assays, including antibody-based assays. In addition, it was well known in the art at the time the invention was made that once an antibody was developed, the antibody could be used with a reasonable expectation of success to detect an antigen on intact cells, as in a buffy coat of whole blood, by either mounting them on slides for immunohistochemical analysis; or by using other techniques well known in the art at the time the invention was made for intact cell analysis with antibodies. Therefore, the invention as a whole

was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

No claims allowed.

This is a continuation of applicant's earlier Application No. 09/554567. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PH.D
PRIMARY EXAMINER 9/16/05